Detailed Title:	A Phase III, randomized, open, controlled, multicenter, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of the meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate noninferiority of coadministration of MenACWY-TT and the 13-valent pneumococcal conjugate vaccine Prevenar 13® versus separate administration of the 2 vaccines
SAP Version:	Version 3
SAP Date:	11-Nov-2016
Scope:	All data pertaining to the above study
Coordinating Author:	PPD
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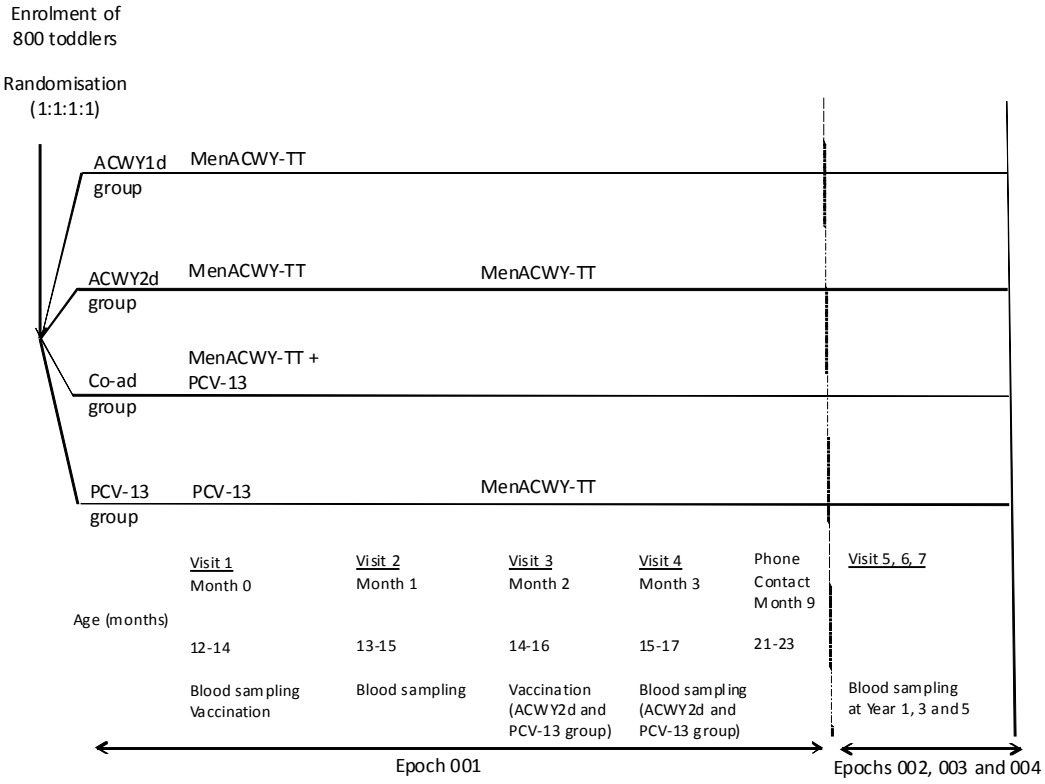
LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ATP	according-to-protocol
CI	confidence interval
CRF	case report form
CSR	clinical study report
DBF	database freeze
ELISA	enzyme-linked immunosorbent assay
GMC	geometric mean concentration
GMT	geometric mean titer
GSK	GlaxoSmithKline
hSBA-MenA	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A
hSBA-MenC	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group C
hSBA-MenW-135	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group W-135
hSBA-MenY	serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group Y
LL	lower limit
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine
NOCI	new-onset chronic illness
OPA	opsonophagocytic activity
PCV13	13-valent pneumococcal conjugate vaccine
rSBA-MenA	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A
rSBA-MenC	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group C
rSBA-MenW-135	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group W-135
rSBA-MenY	serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group Y
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
UL	upper limit

1. DOCUMENT HISTORY

Date	Description	Protocol Version
16-Jan-2015	GSK Version 1	Amendment 1 – 02-Jul-2014
25-Jan-2015	GSK Version 2 New elimination codes are included to be able to eliminate subjects for which concomitant vaccination were reported in the case report form (CRF) after database freeze (DBF) for the primary analysis.	Amendment 1 – 02-Jul-2014
11-Nov-2016	Version 3 Revised per Pfizer standards. Specifications for Month 0 through Month 9 analyses were not changed because GlaxoSmithKline (GSK) previously performed those analyses. "Total cohort Year X" is relaxed to include all subjects who were vaccinated and return for Year X, even if no data concerning persistence endpoint measures are available, although the protocol defines this cohort to include all subjects who were vaccinated and have persistence endpoint measures available in Year X. This expanded definition will enhance analysis of disposition because it provides a cohort that includes all returning subjects, regardless of immunogenicity status.	Amendment 2 – 25-Jan-2016

2. STUDY DESIGN



- **Experimental design:** Phase 3, open-label, randomized, controlled, multicenter study with 4 parallel vaccine groups.
- **Duration of the study:** 62 months for each subject:
  - Epoch 001: Primary starting at Visit 1 (Month 0) and ending at the phone contact (Month 9)
  - Epoch 002: Persistence Visit 5 ending Year 1
  - Epoch 003: Persistence Visit 6 ending Year 3
  - Epoch 004: Persistence Visit 7 ending Year 5
- **Control:** Active control.
- **Vaccine allocation:** Randomized.
- **Blinding:** Open-label.

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- The subsets that are used for antibody titer determination are given below:

Subset name	Description	Definition
Subset 1	Vaccine groups ACWY1d and ACWY2d: hSBA-MenA and hSBA-MenC	The first 50% of enrolled subjects within each country (according to their enrollment date) for vaccine groups ACWY1d and ACWY2d will be tested for hSBA-MenA and hSBA-MenC at all blood sampling time points planned for each vaccine group (ie, Visits 1, 2, 5, 6, and 7 for the ACWY1d vaccine group and Visits 1, 2, 4, 5, 6, and 7 for the ACWY2d vaccine group).
Subset 2	Vaccine groups ACWY1d and ACWY2d: hSBA-MenW-135 and hSBA-MenY	The remaining 50% of enrolled subjects within each country (according to their enrollment date) for vaccine groups ACWY1d and ACWY2d will be tested for hSBA-MenW-135 and hSBA-MenY at all blood sampling time points planned for each vaccine group (ie, Visits 1, 2, 5, 6, and 7 for the ACWY1d vaccine group and Visits 1, 2, 4, 5, 6, and 7 for the ACWY2d vaccine group).
Subset 3	Vaccine groups Co-ad and PCV13: OPA 3, 4, 6B, 14, and 23F	The first 50% of enrolled subjects within each country (according to their enrollment date) for vaccine groups Co-ad and PCV13 will be tested for opsonophagocytic activity (OPA) for pneumococcal serotypes 3, 4, 6B, 14, and 23F at Visits 1 and 2.
Subset 4	Vaccine groups Co-ad and PCV13: OPA 1, 5, 6A, 7F, 9V, 18C, 19A, and 19F	The remaining 50% of enrolled subjects within each country (according to their enrollment date) for vaccine groups Co-ad and PCV13 will be tested for OPA for pneumococcal serotypes 1, 5, 6A, 7F, 9V, 18C, 19A, and 19F at Visits 1 and 2.

The following vaccine group names will be used for the statistical analyses:

Vaccine group order in tables	Vaccine group label in tables	Vaccine group definition for footnote	Pooled vaccine groups label in tables	Pooled definition for footnote
1	ACWY1d	Subjects who received 1 dose of MenACWY-TT at Month 0	Pool1d	Subjects receiving MenACWY-TT at Month 0 only or at Month 0 and Month 2
2	ACWY2d	Subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2	Pool1d	Subjects receiving MenACWY-TT at Month 0 only or at Month 0 and Month 2
3	Co-ad	Subjects who received 1 dose of MenACWY-TT and 1 dose of Prevenar 13 at Month 0		
4	PCV13	Subjects who received 1 dose of Prevenar 13 at Month 0 and 1 dose of MenACWY-TT at Month 2		

The following subgroups, based on the country in which the subject is enrolled, will be used in analyses of demography, reactogenicity, and immunogenicity:

Subgroup order in Tables	Subgroup label in Tables
1	Australia
2	Canada
3	Czech Republic
4	Panama
5	South Africa
6	Turkey

The following subgroups, defined based on the number of doses of Prevenar 13 received before the study start (2 or 3 doses), will be used in analyses of demography, reactogenicity, and immunogenicity:

Subgroup order in Tables	Subgroup label in Tables	Subgroup definition for Footnote
1	2 doses of PCV13	Subjects received 2 doses of Prevenar 13 before the study start
2	3 doses of PCV13	Subjects received 3 doses of Prevenar 13 before the study start

3. OBJECTIVES

3.1. Primary Objectives

3.1.1. Exploratory Primary Objectives

- One (1) month after administration of meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT) in the ACWY1d vaccine group and the ACWY2d vaccine group:

    - To evaluate the immunogenicity of MenACWY-TT after administration of 1 dose in vaccine groups ACWY1d and ACWY2d or 2 doses in vaccine group ACWY2d with respect to serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* groups A, C, W-135, and Y (rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY) titers.

- One (1), 3, and 5 years after the last vaccination in the ACWY1d vaccine group and the ACWY2d vaccine group:

    - To evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers.

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3.1.2. Confirmatory Primary Objectives

The confirmatory primary objectives will be assessed in a hierarchical manner according to the order presented below. The second confirmatory primary objective can only be considered as met if the statistical criteria for both that objective and the first confirmatory primary objective are met.

- To demonstrate the noninferiority of the immune response to MenACWY-TT when coadministered with Pfizer's 13-valent pneumococcal vaccine, Prevenar 13®, versus MenACWY-TT given alone 1 month after vaccination.

Criterion for noninferiority of meningococcal groups A, C, W-135, and Y:

Noninferiority will be demonstrated for each group separately if the lower limit of the 2-sided standardized asymptotic 95% confidence interval (CI) for the group difference between the Co-ad group and the Pool1d group (Co-ad group minus Pool1d group) in the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 is greater than or equal to -10%.

- To demonstrate the noninferiority of the immune response to Prevenar 13 when coadministered with MenACWY-TT versus Prevenar 13 given alone 1 month after vaccination.

Criterion for noninferiority of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F:

Noninferiority will be demonstrated for each serotype separately if the lower limit of the 95% CI of the geometric mean concentration (GMC) ratio between the Co-ad group and the PCV13 group (Co-ad group over PCV13 group) is above 0.5.

3.2. Secondary Objectives

One (1) month after administration of MenACWY-TT in the ACWY1d vaccine group and the ACWY2d vaccine group:

- To evaluate the immunogenicity of MenACWY-TT after administration of 1 dose in vaccine groups ACWY1d and ACWY2d or 2 doses in vaccine group ACWY2d with respect to serum bactericidal assay using human complement to measure activity against *N meningitidis* groups A, C, W-135, and Y (hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY) titers in a subset of subjects.

One (1) month after administration of MenACWY-TT in the Co-ad vaccine group and the PCV13 vaccine group:

- To evaluate the immunogenicity of MenACWY-TT when administered as 1 dose with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers.

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One (1) month after administration of Prevenar 13 in the Co-ad vaccine group and the PCV13 vaccine group:

- To evaluate the immune response to Prevenar 13 coadministered with MenACWY-TT and Prevenar 13 administered alone with respect to antibody concentrations and titers against pneumococcal serotype-specific polysaccharides.

One (1), 3, and 5 years after the last vaccination in the ACWY1d vaccine group and the ACWY2d vaccine group:

- To evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT with respect to hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers in a subset of subjects.

One (1), 3, and 5 years after the last vaccination in the Co-ad vaccine group and the PCV13 vaccine group:

- To evaluate the long-term persistence of the immune response induced by 1 dose of MenACWY-TT with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers.

After each vaccine administration:

- To evaluate the safety and reactogenicity in terms of solicited events, unsolicited adverse events (AEs), serious adverse events (SAEs) and new-onset chronic illnesses (NOCIs) following each study vaccine dose.

One (1), 3, and 5 years after the last vaccination:

- To evaluate the occurrence of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy (ie, meningococcal disease).

4. ENDPOINTS

4.1. Primary Endpoints

- Immunogenicity with respect to components of the study vaccines:

Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 one month after administration of 1 dose of MenACWY-TT in the ACWY1d, ACWY2d, and Co-ad vaccine groups and 1 month after administration of 2 doses in the ACWY2d vaccine group.

  - Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 and geometric mean titers (GMTs) at Years 1, 3, and 5 in the ACWY1d and ACWY2d vaccine groups.

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- Anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F geometric mean antibody concentrations 1 month after administration of Prevenar 13 in the Co-ad and PCV13 vaccine groups.

4.2. Secondary Endpoints

- Immunogenicity with respect to components of the study vaccines:
  - Percentages of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 and ≥1:8 and GMTs 1 month after administration of 1 dose of MenACWY-TT in a subset of subjects in the ACWY1d and ACWY2d vaccine groups and 1 month after administration of 2 doses in the ACWY2d vaccine group.
  - Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 and GMTs 1 month after administration of 1 dose of MenACWY-TT in the PCV13 vaccine group.
  - Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:128 and GMTs 1 month after administration of 1 dose of MenACWY-TT in the ACWY1d, ACWY2d, and Co-ad vaccine groups.
  - Percentages of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 and ≥1:8 and GMTs at Years 1, 3, and 5 in a subset of subjects in the ACWY1d and ACWY2d vaccine groups.
  - Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 and GMTs at Years 1, 3, and 5 in the Co-ad and PCV13 vaccine groups.
  - Percentages of subjects with anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F antibody concentrations ≥0.15μg/mL, ≥0.26μg/mL, and ≥0.35μg/mL 1 month after administration of Prevenar 13 in the Co-ad and PCV13 vaccine groups.
  - Percentages of subjects with anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F OPA titers ≥1:8 and GMTs 1 month after administration of Prevenar 13 in the Co-ad and PCV13 vaccine groups.
- Solicited local and general events:
  - Occurrence of each solicited local and general event within 4 days (Day 0 – Day 3) after each study vaccination.

- Unsolicited AEs:
  - Occurrence of unsolicited AEs within 31 days (Day 0 – Day 30) after any study vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs:
  - Occurrence of SAEs from Month 0 to Month 9.
- SAEs related to study vaccine administration:
  - Occurrence of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy (ie, meningococcal disease) from the first receipt of study vaccine until study end.
- Occurrence of NOCIs:
  - Occurrence of NOCIs (eg, asthma, autoimmune disorders, type 1 diabetes, allergies) from Month 0 to Month 9.

5. STUDY POPULATIONS

Eight (8) cohorts are defined for the purpose of analyses. The definitions of the cohorts are given below:

5.1. Total Vaccinated Cohort

The total vaccinated cohort will include all subjects vaccinated with at least 1 dose of study vaccine.

The total vaccinated cohort analyses will be performed per vaccine actually administered at Dose 1.

5.2. According-to-protocol (ATP) Cohort for Safety

The ATP cohort for analysis of safety will include all vaccinated and eligible subjects:

- who meet all inclusion criteria and no exclusion criteria for the study.
- who have received at least 1 dose of study vaccine according to their random assignment.
- for whom administration site and route of study vaccine is known and according to protocol.
- who have not received the booster dose of Prevenar 13 outside the defined timeline (if administered, for vaccine groups ACWY1d and ACWY2d only).

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- who have not received a vaccine forbidden in the protocol (subjects who received a vaccine not foreseen by the study protocol from 30 days before until 30 days after the administration of 1 [or more] of the study vaccine doses will be eliminated from the ATP cohort for safety if the vaccine not foreseen by the protocol was administered before the corresponding postvaccination blood sample).

- who have not received a meningococcal or pneumococcal vaccine not foreseen in the protocol, with the exception of the booster dose of Prevenar 13 in the ACWY1d and ACWY2d vaccine groups.

5.3. According-to-protocol Cohort for Immunogenicity after Dose 1

The ATP cohort for immunogenicity after Dose 1 will include all evaluable subjects (ie, those meeting all eligibility criteria, complying with the procedures defined in the protocol, and with no exclusion criteria during the study) from the ATP cohort for safety:

- who received all study vaccines at Month 0.

- for whom assay results are available with antibodies against at least 1 study vaccine antigen component at Visit 2.

  Note: For the PCV13 vaccine group, subjects with an available blood sample at Visit 2 will be included in the ATP cohort for immunogenicity after Dose 1.

- who comply with the procedures and intervals defined in the protocol:

  - Date of birth to Vaccination 1 (Visit 1): 12 to 14 months.

  - Blood sample at Visit 1 to Vaccination 1 (Visit 1): at least 0 days (evaluation on case-by-case basis).

  - Vaccination 1 (Visit 1) to blood sample at Visit 2: 21 to 48 days.

- who have no concomitant infection that may influence immune response.

- who were not administered a vaccine not foreseen by the study protocol before the corresponding postvaccination blood sample.

5.4. According-to-protocol Cohort for Immunogenicity after Dose 2

The ATP cohort for immunogenicity after Dose 2 will include all evaluable subjects (ie, those meeting all eligibility criteria, complying with the procedures defined in the protocol, and with no exclusion criteria during the study) from the ACWY2d and PCV13 vaccine groups in the ATP cohort for safety:

- who received all study vaccines at Month 0 and Month 2.

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- for whom assay results are available with antibodies against at least 1 study vaccine antigen component at Visit 4.
- who comply with the procedures and intervals defined in the protocol:
  - Date of birth to Vaccination 1 (Visit 1): 12 to 14 months.
  - Blood sample at Visit 1 to Vaccination 1 (Visit 1): at least 0 days (evaluation on case-by-case basis).
  - Vaccination 1 (Visit 1) to Vaccination 2 (Visit 3): 60 to 90 days.
  - Vaccination 2 (Visit 3) to blood sample at Visit 4: 21 to 48 days.
- who have no concomitant infection that may influence immune response.
- who were not administered a vaccine not foreseen by the study protocol before the post-Dose 2 blood sample.

5.5. Total Cohort Year X

The total cohort Year X will include all subjects who were both vaccinated and who return for Year X. "Year X" will refer to Year 1, Year 3, or Year 5.

5.6. According-to-protocol Cohort for Persistence at Year X

"Year X" will refer to Year 1, Year 3, or Year 5. The ATP cohort for persistence at Year X will include all subjects:

- who meet all eligibility criteria.
- who have received the complete primary vaccination series with MenACWY-TT according to their random assignment.
- who have assay results available for at least 1 antigen tested at the respective year (ie, Year X).
- who comply with the procedures and intervals defined in the protocol (refer to Section 5.5 of the protocol).
- who did not receive a product leading to exclusion from an ATP analysis as listed in Section 6.7.2 of the protocol.
- who did not present with a medical condition leading to exclusion from an ATP analysis as listed in Section 6.8 of the protocol.

- who were not excluded from the ATP cohort for immunogenicity (after Dose 1 for the ACWY1d and Co-ad vaccine groups; after Dose 2 for the ACWY2d and PCV13 vaccine groups) and from the previous ATP cohorts for persistence (for Years 3 and 5 only) unless the reason for exclusion was either noncompliance with the protocol-defined serum sampling windows or lack of availability of immunogenicity results at the previous time point.

5.7. Adapted ATP Cohort

When presenting different time points, the adapted ATP cohort will be used to denote that, for each time point, the corresponding ATP cohort for immunogenicity/persistence has been used.

More specifically,

- the analyses on the pre– and post–Dose 1 time points will be based on the ATP cohort for immunogenicity after Dose 1.

- the analyses on the post–Dose 2 time point will be based on the ATP cohort for immunogenicity after Dose 2.

- the analysis on the Year 1, 3, and 5 time points will be based on the ATP cohort for persistence at Year 1, 3, and 5, respectively.

5.8. Adapted Total Cohort

When jointly presenting different time points, the adapted total cohort will be used to denote that, for each time point, the corresponding total cohort has been used.

More specifically,

- the analyses on the pre–Dose 1, post–Dose 1, and post–Dose 2 time points will be based on the total vaccinated cohort.

- the analyses on Year 1, 3, and 5 time points will be based on the total cohort Year 1, 3, and 5, respectively.

Note: The first analysis included the enzyme-linked immunosorbent assay (ELISA) results for MenACWY-TT up to Month 1 for the ACWY1d and Co-ad vaccine groups and up to Month 3 for the ACWY2d and PCV13 vaccine groups in order to analyze the immunogenicity endpoints related to MenACWY-TT as well as safety and reactogenicity for all vaccine groups up to Month 3. A second database cleaning was performed before the analysis of the immunogenicity endpoints related to PCV13 and the Month 9 safety follow-up. During this cleaning, GSK noticed that for some subjects concomitant vaccinations were reported after the DBF date for the first analysis, and these subjects need to be excluded from the ATP cohorts.

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In order to exclude these subjects from the ATP cohorts and to maintain the possibility of regenerating the results published in the main study report, new elimination codes were introduced in the study. These new elimination codes R1 and R2 will be used for the reanalysis of immunogenicity related to MenACWY-TT and the new analysis will be included in an amendment to the main study report. They will also be used in the analysis of immunogenicity endpoints related to PCV13 and the Month 9 safety follow-up.

6. STATISTICAL METHODS

6.1. Analysis of Primary Vaccination

6.1.1. Demography

Demographic characteristics (age [in months, with range and standard deviation (SD)] at vaccination at Visit 1, sex, geographic ancestry, and ethnicity) of each study cohort will be tabulated per vaccine group.

The summary of number of doses of Prevenar 13 received before study start will also be tabulated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per vaccine group.

The following demography analyses will also be performed overall, by country, and by the number of doses of Prevenar 13 received before the study (2 or 3 doses):

- Demographic characteristics (age [in months, with range and SD] at vaccination at Visit 1, sex, geographic ancestry, and ethnicity) will be tabulated for the ATP cohort for immunogenicity.

- Summary of subjects enrolled into the study and excluded from ATP analyses along with reasons for exclusion.

- Number of subjects vaccinated, withdrawn, and completed with reasons for withdrawal.

6.1.2. Analysis of Immunogenicity

The primary analysis of immunogenicity will be performed on the adapted ATP cohort. At the post–Dose 1 time point, the analysis will be done on the ATP cohort for immunogenicity after Dose 1. At the post–Dose 2 time point, the analysis will be done on the ATP cohort for immunogenicity after Dose 2.

A second analysis on the total vaccinated cohort will be performed to support the ATP analysis if:

- the percentage of subjects enrolled in groups Co-ad or ACWY1d with serological results at Visit 2 excluded from the ATP cohort for immunogenicity after Dose 1 is more than 5% or

- the percentage of subjects enrolled in groups ACWY2d or PCV13 with serological results at Visit 4 excluded from the ATP cohort for immunogenicity after Dose 2 is more than 5%.

6.1.2.1. Within Vaccine Group

For the ACWY1d, ACWY2d, Co-ad, and PCV13 vaccine groups, at each time point that data on meningococcal antibody titers, antipneumococcal antibody concentrations, or pneumococcal antibody titers are available:

- Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 will be calculated.

- Percentages of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 and ≥1:8 will be calculated.

- Percentages of subjects with anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F antibody concentrations ≥0.15μg/mL, ≥0.26μg/mL, and ≥0.35μg/mL will be calculated.

- Percentages of subjects with anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F OPA titers ≥1:8 will be calculated.

- GMTs and GMCs with 95% CIs will be calculated.

- The distribution of antibody concentrations and titers will also be tabulated and evaluated using reverse cumulative distribution curves.

In addition, the following analyses will also be performed by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses):

- Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 will be calculated.

- Percentages of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 and ≥1:8 will be calculated.

- Percentages of subjects with anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F antibody concentrations ≥0.15μg/mL, ≥0.26μg/mL, and ≥0.35μg/mL will be calculated.

- Percentages of subjects with anti–pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F OPA titers ≥1:8 will be calculated.

- GMTs and GMCs with 95% CIs will be calculated.

6.1.2.2. Between Vaccine Groups

Confirmatory Primary Objectives

Noninferiority of MenACWY-TT when coadministered with Prevenar 13 versus MenACWY-TT given alone 1 month after vaccination.

- Two (2)-sided standardized asymptotic 95% CI of the vaccine group difference between the Co-ad and the Pool1d vaccine groups (Co-ad vaccine group minus Pool1d vaccine group) will be computed for the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titer ≥1:8 (Visit 2).

It can be concluded (for each meningococcal group separately) that coadministration of MenACWY-TT and Prevenar 13 is noninferior to administration of MenACWY-TT alone if the lower limit of the CI of the difference is greater than or equal to -10%.

Noninferiority of Prevenar 13 when coadministered with MenACWY-TT versus Prevenar 13 given alone 1 month after vaccination.

- 95% CI of the GMC ratio between the Co-ad and the PCV13 vaccine groups (Co-ad vaccine group over PCV13 vaccine group) will be computed for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (Visit 2). This will be performed using an analysis of covariance (ANCOVA) model on the logarithm_{10} transformation of the concentrations using the prevaccination logarithm_{10} transformation of the concentrations, the country, the number of doses of Prevenar 13 received before the study (2 or 3 doses), and the vaccine group as covariates.

It will be concluded (for each serotype separately) that coadministration of Prevenar 13 and MenACWY-TT is noninferior to administration of Prevenar 13 alone if the lower limit of the CI of the GMC ratio is above 0.5.

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Exploratory Analysis

An exploratory evaluation of the comparability of the immune response to each pneumococcal serotype at 1 month after administration of Prevenar 13 will be done through:

- Computation of the asymptotic standardized 95% CI on the difference between the percentages of subjects with antibody concentrations and OPA titers above proposed cutoffs between the vaccine groups Co-ad and (minus) PCV13 (Visit 2).

- Computation of the 95% CI of the GMC and GMT ratios between the Co-ad and (over) the PCV13 vaccine groups (Visit 2). This will be performed using an ANCOVA model on the logarithm_{10} transformation of the concentrations/titers using the prevaccination logarithm_{10} transformation of the concentrations or titers, the country, the number of doses of Prevenar 13 received before the study (2 or 3 doses), and the vaccine group as covariates.

An exploratory evaluation of the comparability of the immune response to each meningococcal group at 1 month after the first dose of MenACWY-TT and at 1 month after the second dose of MenACWY-TT will be done through:

- Computation of the asymptotic standardized 95% CI on the difference between the percentage of subjects with rSBA and hSBA titers above proposed cutoffs between the ACWY2d vaccine group (after the second dose of MenACWY-TT, Visit 4) and (minus) the ACWY1d vaccine group (Visit 2).

- Computation of the 95% CI of the rSBA and hSBA GMT ratios between the ACWY2d vaccine group (after the second dose of MenACWY-TT, Visit 4) and (over) the ACWY1d vaccine group (Visit 2). This will be performed using an ANCOVA model on the logarithm_{10} transformation of the titers using the prevaccination logarithm_{10} transformation of the titers, the country, the number of doses of Prevenar 13 received before the study (2 or 3 doses), and the vaccine group as covariates.

- These analyses will be performed on the adapted ATP cohort.

6.1.3. Analysis Of Safety

The primary analysis will be performed on the total vaccinated cohort. If, for any vaccine group, more than 5% of the enrolled subjects are eliminated from the ATP cohort for safety, then a second analysis will be performed on the ATP cohort for safety to support the analyses of the total vaccinated cohort.

All percentages/proportions described below will be tabulated with exact 95% CIs.

Timing between reconstitution of and vaccination with MenACWY-TT will be summarized per vaccine group and overall.

The percentages of subjects with at least 1 local event (solicited and unsolicited), with at least 1 general event (solicited and unsolicited), and with any event or AE during the 4-day solicited follow-up period will be tabulated. The same calculations will be performed for events rated as Grade 3 and for events related to vaccination.

The percentage of subjects reporting each individual solicited local (any grade, Grade 3, and requiring medical advice) and general (any grade, Grade 3, related, Grade 3 and related, and requiring medical advice) event during the 4-day follow-up period (Day 0 – Day 3) after vaccination will be tabulated. Occurrence of fever will also be reported per 0.5°C cumulative increments up to >40.0°C. All of the above calculations will also be performed by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses).

The percentages of subjects using concomitant medication (any medication, any antipyretic, any antipyretic taken prophylactically, respectively) during the 4-day and 31-day follow-up periods (Day 0 – Day 3 and Day 0 – Day 30, respectively) after each vaccination will be summarized.

The verbatim reports of unsolicited AEs will be reviewed by the medical monitor and the signs and symptoms will be coded according to MedDRA terminology.

The percentages of subjects with unsolicited AEs within 31 days after vaccination (Day 0 – Day 30) will be tabulated by vaccine group and by MedDRA preferred term. Similar tabulations will also be performed by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses). Likewise, tabulations by vaccine group and MedDRA preferred term will also be done for Grade 3 unsolicited AEs, for unsolicited AEs possibly related to vaccination, and for Grade 3 unsolicited AEs possibly related to vaccination.

SAEs, withdrawals due to AE(s), and large swelling reactions will be described in detail. Similar calculations will also be performed by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses).

The numbers and percentages of subjects with SAEs and NOCIs (eg, autoimmune disorders, asthma, type 1 diabetes, and allergies) will be tabulated with exact 95% CIs by vaccine group. Similar calculations will also be performed by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses).

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6.2. Analysis Of Persistence

6.2.1. Demography

Demographic characteristics (age [in months, with range and SD] at Years 1, 3, and 5, sex, geographic ancestry, ethnicity, and months since the last dose of vaccine) for each study cohort will be tabulated per vaccine group.

The distribution of subjects enrolled at Years 1, 3, and 5 among the study sites will be tabulated as a whole and per vaccine group and the reasons for not attending a visit at Years 1, 3, and 5 among all vaccinated subjects will be summarized.

The following demographic analyses will also be performed overall and by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses):

- Demographic characteristics (age [months] at Visit 1 given that the subject attended Year X, age [in months, with range and SD] at Years 1, 3, and 5, sex, geographic ancestry, ethnicity, and months since the last dose of vaccine) will be tabulated per vaccine group for the ATP cohort for persistence.

- Distribution of subjects among study sites.

- Reasons for not attending Year X.

- Summary of subjects enrolled into the study and excluded from ATP analyses along with reasons for exclusion.

6.2.2. Analysis of Persistence at Year 1, 3, and 5

For each Year 1, 3, and 5: the analysis of antibody persistence will be based on the ATP cohort for persistence for that year. If for any vaccine group, at any time point, the percentage of subjects with serological results excluded from the ATP cohort is higher than 5%, a second analysis based on the total cohort (ie, total cohort Year X) will be performed to complement the ATP analysis.

6.2.2.1. Within-vaccine-group Analysis

For the ACWY1d, ACWY2d, Co-ad, and PCV13 vaccine groups for each antigen assessed at each blood sampling time point:

- Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 will be calculated.

- Percentages of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 and ≥1:8 will be calculated.

- GMTs with 95% CIs will be calculated.

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- The distribution of antibody titers will also be tabulated and evaluated using reverse cumulative distribution curves.

In addition to the overall analyses, the following analyses of persistence on the ATP cohort for persistence at Year 1, 3, and 5 will also be performed by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses):

- Percentages of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 and ≥1:128 will be calculated.

- Percentages of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 and ≥1:8 will be calculated.

- GMTs with 95% CIs will be calculated.

6.2.2.2. Modeling Prediction

In order to complement the descriptive analyses of observed persistence per time point, longitudinal analyses will be performed after Year 5 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY. These analyses will include all results from Month 0 up to Year 5 and will be performed on the adapted ATP cohort.

A longitudinal model taking into account the vaccine group and all available immunogenicity time points from the beginning until the last time point will be fitted. This model will be primarily aimed at evaluating the selection effect in the vaccine group. Time points will be considered as categorical.

For a specific assay, the model will include assay results from a time point provided that these were part of the ATP cohort for that time point. Results below cutoff will be set at half the value of the cutoff. The model will be fitted via the proc mixed procedure according to the following code:

```
Model 1 - Repeated model on all available time points
PROC MIXED data=sero ;
CLASS group time;
  MODEL log_val = group | time ;
  Repeated time / TYPE=UN SUBJECT=pid;
RUN;
```

Per Section 10.7.3 of the protocol, "a longitudinal analysis will be performed after Year 5. These analyses will include all results from Month 0 up to Year 5 and will be performed on the ATP cohort for immunogenicity adapted per time point and the ATP cohort for persistence at Year 1, 3, and 5, respectively." So the modeling prediction will also be performed for the ATP cohorts for persistence at Years 1, 3, and 5. The analysis of the ATP cohort for persistence at Year X will include data from Year >X if available for eligible subjects. These analyses will be performed only after Year 5.

[redacted]

[redacted]

6.2.3. Analysis of Safety

SAEs considered related to vaccination, related to lack of vaccine efficacy, related to study procedures, or leading to withdrawal of the subject from the study will be tabulated for Years 1, 3, and 5.

The analysis will be performed overall, by country, and by the number of doses of Prevenar 13 received before the study (2 or 3 doses).

7. STATISTICAL CALCULATIONS

7.1. Derived and Transformed Data

- The SAS code for calculating age in years will be INT(INTCK("MONTH", birth date, vaccination date)/12).
- Duration from the last primary vaccination to any persistence time point will use the day of primary vaccination as Day 0.
- Activity date is defined as the date associated with any activity performed at the indicated visit.
- If a percentage calculation has no eligible subjects, then the sample size will be "0" and the percent value will be ".".

7.1.1. Immunogenicity

- The cutoff value is defined by the laboratory before the analysis and is described in Section 5.7.3 of the protocol.
- The GMT/GMC calculations are performed by taking the antilog of the mean of the log titer/concentration transformations. Antibody titers/concentrations below the cutoff of the assay will be given an arbitrary value of half the cutoff for the purpose of GMT/GMC calculation.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or nonevaluable measurements will not be replaced.

7.1.2. Safety and Reactogenicity

- For a given subject and the analysis of solicited events within 4 days after vaccination, missing or nonevaluable measurements will not be replaced. Therefore, the analysis of the solicited events based on the total vaccinated cohort will include only vaccinated subjects for doses with documented safety data (ie, event screen completed). More specifically, the following rules will be used:
  - Subjects who documented the absence of a solicited event after 1 dose will be considered not having that event after that dose.

[redacted]

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- Subjects who documented the presence of a solicited event and fully or partially recorded daily measurements over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.

- Subjects who documented the presence of a solicited event after 1 dose without having recorded any daily measurements will be assigned to the lowest intensity category at that dose (ie, 37.5°C for fever or Grade 1 for other events).

- Doses without symptom sheets documented will be excluded.

- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication.

- For the analysis, rectal temperatures will be coded as follows:

Grade	**Temperature**
0	<38.0°C
1	≥38.0°C - ≤39.0°C
2	>39.0°C - ≤40.0°C
3	>40.0°C

When temperature is measured by the oral, axillary, or tympanic route, the corresponding rectal temperature will be derived by adding 0.5°C to the temperature recorded. The above intensity grade will be applied to the derived rectal temperature.

- The way the percentage of subjects will be derived will depend on the event analyzed (see table below for details). As a result, the N value will differ from one table to another.

Analysis	**N used for deriving % per subject for vaccination phase**
Concomitant vaccination	All subjects with study vaccine administered
Solicited general event	All subjects with at least 1 solicited general event documented as either present or absent (ie, event screen completed)
Solicited local event	All subjects with at least 1 solicited local event documented as either present or absent (ie, event screen completed)
Unsolicited adverse event	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

7.2. Sensitivity Analyses

- In case the number of subjects who documented the presence of a solicited event after 1 dose without having recorded any daily measurement exceeds 1%, a sensitivity analysis will be carried out to assess the impact of assigning the lowest intensity for the event. Two (2) additional analyses will be performed for solicited events collected during the 4-day (Day 0 – Day 3) follow-up period:

  – In the first sensitivity analysis, subjects who documented the presence of an event without having recorded any daily measurement will be assigned to the highest intensity category (ie >39.5°C for fever or Grade 3 for other events), while the subjects without documentation will be excluded.

  – In the second sensitivity analysis, both subjects who documented the presence of an event without having recorded any daily measurement and subjects without documentation will be excluded.

7.3. Data Presentation Description

The following decimal description will be used for the demography, immunogenicity, and safety/reactogenicity analyses:

Display Table	Parameters	Number of decimal Digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
rSBA-MenA	GMT	1
rSBA-MenC	GMT	1
rSBA-MenW-135	GMT	1
rSBA-MenY	GMT	1
hSBA-MenA	GMT	1
hSBA-MenC	GMT	1
hSBA-MenW-135	GMT	1
hSBA-MenY	GMT	1
Pneumococcal vaccine serotypes (ELISA)	GMC	2
Pneumococcal vaccine serotypes (OPA)	GMT	1
Immunogenicity	Ratio of GMT/GMC	2
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

Abbreviations: ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMT = geometric mean titer; LL = lower limit; OPA = opsonophagocytic activity; UL = upper limit.

7.4. Methodology for Computing CI

- All CIs computed will be 2-sided 95% CIs.

- The exact 95% CIs for a proportion within a group will be based on the method by Clopper and Pearson (Clopper and Pearson, 1934).[1]

- The standardized asymptotic 95% CI for the group difference in proportions will be based on method 6 described by Newcombe (Newcombe, 1998).[2]

- The 95% CI for GMTs/GMCs will be obtained within each vaccine group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential transformation of the 95% CI for the mean of log-transformed titer/concentration.

- The 95% CIs of the vaccine group GMC/GMT ratios will be computed using an ANCOVA model on the logarithm_{10} transformation of the concentrations/titers. The ANCOVA model will include the prevaccination logarithm_{10} transformation of the concentration/titers, country, number of doses of Prevenar 13 received before the study (2 or 3 doses), and vaccine group as covariates.

8. CONDUCT OF ANALYSES

8.1. Sequence of Analyses

Statistical analyses will be done stepwise:

- A first analysis will include the data collected up to Month 1 for the ACWY1d and Co-ad vaccine groups and Month 3 for the ACWY2d and PCV13 vaccine groups in order to analyze the immunogenicity endpoints related to MenACWY-TT, solicited events during the 4-day (Day 0-3) period after each vaccine dose, unsolicited AE during the 31-day (Day 0-30) period after each vaccine dose, and SAEs (the safety analysis includes both MenACWY-TT and PCV13 vaccines). The analyses will be performed on data as clean as possible.

- A second analysis will include the data collected up to Month 1 for the Co-ad vaccine group and Month 3 for the PCV13 vaccine group in order to analyze the immunogenicity endpoints related to PCV13. This analysis will also include the SAEs and NOCIs reported from administration of the first study vaccine dose until Month 9. If unsolicited AE that occurred during the 31-day (Day 0-30) period are encoded after the first analysis was performed, unsolicited AE will be analyzed again in the second analysis. These analyses will be performed on data as clean as possible.

- Further analyses will be done at the end of epochs 002, 003, and 004 and these will include data on immunogenicity endpoints. In addition, the SAEs of epoch 001 and SAEs considered related to vaccination of epochs 002, 003, and 004 will be analyzed.

[redacted]

[redacted]

The analyses of epochs 002 and 003 will be done on data as clean as possible and the analyses of epoch 004 will be done on clean data.

8.2. Statistical Considerations for Interim Analyses

No interim analysis will be performed.

9. CHANGES FROM PLANNED ANALYSES

Please note that the changes from the planned analysis to be included in the clinical study report (CSR) will be identified during the CSR review.

- Demographic characteristics will also include summary of ethnicity.
- Timing between reconstitution of and vaccination with MenACWY-TT will be summarized per vaccine group and overall.
- Changes are made in analysis by country and by the number of doses of Prevenar 13 received before the study (2 or 3 doses).
- The adapted ATP cohort and adapted total cohort are defined in detail.
- In addition to criteria mentioned in the protocol for the evaluation of subjects to be included in the ATP cohorts for analysis of immunogenicity after Dose 1 and after Dose 2, 1 more criterion, "blood sample at Visit 1 to Vaccination 1 (Visit 1): at least 0 days (evaluation on case-by-case basis)" has been added since in previous studies in many cases subjects were vaccinated before the prevaccination blood sample was taken or the prevaccination blood sample was not taken at all or the blood sample was taken several days later, and these incidences will have an impact on subject immune response and results. Therefore, any deviation from the time of prevaccination blood sample and first vaccination stated in the protocol and its impact on the immune response needs to be evaluated.
- Because of unavailability of PCV13 data at the time of the first analysis, the ATP cohort for immunogenicity after Dose 1 for the PCV13 vaccine group will include all subjects with a blood sample available at Visit 2. The same ATP cohort will be used for analysis of PCV13 data when the results are available. Since all the analysis is done on the subjects with available results only, if the subjects included in the PCV13 vaccine group do have available blood samples but do not have PCV13 results available, this will not affect the analysis.

10. REFERENCES

1 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4):404-13.

2 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873-90.